REVIEW ARTICLE

Early stage breast cancer and radiotherapy: update

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Summary

Breast cancer (BC) is the most common malignancy among women. Therapeutic options are based on disease staging, histopathological characteristics, age, and others. The objective of the present study is to carry out an update of the concepts and definitions of radiotherapy (RT) in conservative treatment of early-stage breast cancer, with emphasis on indications, contraindications, RT dose fractionation schedules (classic, hypofractionated and partial breast irradiation), adjuvant RT in ductal carcinoma in situ (DCIS) and molecular predictors of recurrence. MEDLINE, SciELO and Cochrane databases were used for article selection. Adjuvant RT is indicated for patients with BC who underwent conservative breast surgery. In selected patients, hypofractionated or partial breast irradiation can be used. Adjuvant RT should be provided for all patients with DCIS. The correlation of RT and molecular predictors of local and systemic recurrence are not yet well-known.

Keywords: Breast neoplasms; radiotherapy; dose fractionation; radiotherapy, adjuvant.

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Introduction

Breast cancer is the most common malignancy among women (with the exception of non-melanoma skin cancers). According to data from the Instituto Nacional do Câncer (INCA), in Brazil, 49,240 new cases were estimated for the year 2010, which corresponds to an estimated risk of 65 new cases per 100,000 women[1].

Early diagnosis is a major prognostic factor and the therapeutic choice will depend on the clinical stage of the disease, pathological characteristics, clinical conditions, age and the patient's wishes.

Tumors staged as 0 (in situ) to IIB are considered as initial breast cancer according to the TNM classification of the American Joint Committee on Cancer.

For many years, the radical mastectomy proposed by Halsted in 1894 was the standard treatment for breast cancer regardless of any associated factors. However, from the 80's on, there was a change in the therapeutic approach, following the trend of more conservative treatments, but without compromising oncological safety.

Breast conservation, which is based on the surgical excision of the tumor (sectorectomy or quadrantectomy) and axillary management (with or without sentinel node axillary dissection) followed by radiotherapy (RT), is now the standard local treatment for the disease in early stages.

This study presents an update of concepts and definitions of radiotherapy (RT) in conservative treatment of early-stage breast cancer with emphasis on indications, contraindications, modalities, dose and fractionation RT (classic scheme, hypofractionated and partial breast irradiation), adjuvant RT in ductal carcinoma in situ and RT association with molecular predictors of recurrence.

Methods

This is an update on the proposed theme using the MEDLINE, SciELO and Cochrane databases. As a search engine, the keywords "breast cancer", "radiotherapy", "early stage" and "conservative treatment" were used for the selection of available key articles, with emphasis on the last 10 years.

Randomized phase III prospective trials were especially considered, as well as those considered fundamental in therapeutic decision-making.

Radiotherapy in the conservative treatment

At least six randomized trials compared radical mastectomy with conservative surgery followed by RT and showed an equivalent overall survival rate between these therapeutic modalities[2]. Updates with twenty years of follow-up of studies from the National Cancer Institute of Milan[3] and the National Surgery Adjuvant Breast and Bowel Project (NSABP) B06[4] corroborated these results.

It is important to emphasize that since these studies were initiated, there has been considerable development in imaging techniques for tumor location, in addition to the recommendation of the requirement to obtain free resection margins in order to reduce the risk of local recurrence, which was previously not considered necessary. Moreover, the use of adjuvant hormone therapy (HT) has reduced the risk of local recurrence and increased survival[5].

Within this rationale, some studies have examined the role of RT after breast-conserving surgery in women with early-stage breast cancer, in order to identify a subgroup of patients that would not benefit from RT after surgery and HT.

A Canadian study[6] randomized 769 patients aged 50 years or more, T1-T2 tumors and negative lymph nodes to receive breast RT and HT with tamoxifen versus HT with tamoxifen. At 5.6 years of median follow-up, it was observed that local recurrence was 0.6% and 7.7% ($p < 0.001$) for the first and second groups, respectively.

The Cancer and Leukemia Group B, Radiation Therapy Oncology Group e Eastern Cooperative Oncology Group[7] randomized 639 patients aged 70 years or more, clinical stage I (T1N0M0), with positive estrogen receptors to receive RT and HT or HT exclusively. There was no difference in distant metastasis and overall survival at five years. There was better local control in patients who received combined adjuvant therapy (local recurrence rate of 1% RT-HT versus 4% HT, $p < 0.001$). Fifty-seven percent of women eligible for the study refused participation, as they did not agree to receive HT without RT. Despite these results, some authors question whether an absolute difference of only 3% in local control rate would justify the cost-benefit of radiotherapy in this group of patients. However, if one takes into account the short follow-up period of this study (5 years) in relation to life expectancy of women of 10 or 15 years, the gain in absolute terms would be more robust.

Furthermore, with the advent of modern RT techniques (tridimensional conformal 3D-CRT - or intensity modulated RT - IMRT) a better sparing of adjacent normal tissues can be achieved (heart, lungs, esophagus, bone and skin) with more homogeneous dose distribution, substantially reducing treatment toxicity[8].

Finally, mastectomy with preservation of the papillary-areola complex, which, despite being defended by some authors as oncological surgery[9] should be considered as conservative (there is no level I evidence yet to ensure the oncological safety of mastectomy with preservation of papillary-areola complex, also called adenomastectomy) therefore, capable of receiving adjuvant RT. In fact, a long-term study of the Karolinska Institute[10] following 12 years of evolution of patients treated with this technique showed a 28% chance of recurrence x 8.5% in favor of patients who received postoperative RT.

Thus, whole breast irradiation is recommended for all women undergoing conservative surgery for breast cancer in initial stages.

Contraindications to conservative treatment

Conservative treatment in breast cancer is possible for most women; however, it is not applicable to all. Contraindications to conservative treatment are subdivided into absolute and relative.

Absolute contraindications

- Persistent positive margins after several attempts at re-excision;
- Multicentric disease – two or more primary tumors in separate quadrants of the breast;
- Microcalcifications with diffuse aspects on the mammography, suggesting multicentricity;
- Pregnancy, although it may be possible to perform a conservative surgery in the last trimester and RT after delivery.

Relative contraindications

- Connective tissue diseases, particularly scleroderma or syndromes that have a high chance of cutaneous involvement (higher rates of dermal complications);
- Large tumor in small breast, when surgery can result in a significant esthetic defect;
- Women with large or pendulous breasts may be submitted to RT as long as it is technically possible to obtain adequate dose homogeneity;
- History of previous RT in the breast region (e.g., Hodgkin's disease or conservative treatment of ipsilateral breast).
- Premenopausal patients who are carriers of the BRCA1/2 mutation.

In many situations, patients that are candidates for conservative treatment are submitted to a radical mastectomy due to the use of inappropriate criteria. Age, histological subtypes, immunohistochemical characteristics, metastasis to axillary lymph nodes and internal mammary chain, tumor location and positive family history do not contraindicate conservative therapy. In addition to these parameters, many patients refuse conservative treatment due to stigma/fear of RT. Nevertheless, removal of patients from their usual activities for 5 or 6 weeks to undergo RT, or the distance from her home to RT service are also variables that influence the patient's therapeutic decision[11].

Radiotherapy modalities, dose and fractionation

Classic scheme

Classically, the modality used for breast RT is teletherapy. There are different dose and fractionation schemes used, although most of the major world centers use from 4500 to 5000 cGy of total dose to 180 to 200 cGy/fraction, 5 days a week.

Using the argumentation that the tumor bed is the site of most local recurrences[12,13] and that greater control could be achieved with a higher dose (booster) in the quadrant initially affected by the tumor (including the surgical scar) with no significant increase in morbidity, this practice began to be considered. The actual impact of the boost in conservative treatment was directly evaluated in two randomized trials.

In the Lyon study[14], 1,024 women with invasive tumors ≤ 3 cm in diameter, submitted to local excision and axillary dissection (98% of negative margins) plus whole breast RT with a dose of 5000 cGy were randomized to receive 1000 cGy boost dose in the tumor bed or no additional treatment. With a median follow-up of 3.3 years, the rate of local failure at 5 years was 3.6% and 4.5%, with and without boost, respectively ($p = 0.044$).

The European Organization for Research and Treatment of Cancer (EORTC)[15] randomized 5,569 women with stage I or II breast cancer who underwent conservative surgery and whole breast RT with a dose of 5000 cGy, between a boost of 1600 to 2600 cGy versus no additional treatment. The rate of local recurrence in five years was significantly lower in women who received boost (4.3% vs. 7.3%) being more significant in women under 45 years (10.2% vs. 19.2%). There were no differences in overall survival and survival free of distant metastases in both groups. At the ten-year update of this study[16], the use of boost maintained the gain of local control benefit (local failure of 10.2% without boost versus 6.2% with it; $p < 0.0001$) in all age groups of the sample.

The boost dose can be delivered with teletherapy or brachytherapy. The first more commonly uses electrons with variable energy, depending on breast size and tumor bed depth; in the latter, Iridium-192 can be used by placing plastic catheters or needles, usually using two plans for complete coverage of the target-volume. They can be placed at the time of surgery, with subsequent loading of radioactive sources. Use of external beam radiation therapy or teletherapy with photons can also be prescribed for boost planning.

The best way to determine the boost location is through visualization of metal clips placed during surgery. In their absence, imaging tests (ultrasound, mammography and/or breast MRI) can be used as a guide to the location of the tumor bed, plus the information of the surgical scar. A common practice is to treat the whole quadrant of the primary lesion site.

Moreover, this is a challenging practice for the Brazilian radiation oncologist, who almost always treats the patient after conservative surgery with immediate reconstruction without proper demarcation by metal clips. The scar reference is lost, as it will not necessarily be in the initially affected quadrant and it is difficult to establish if the margin of the parenchyma to receive a boost dose is still in the projection of the quadrant in question.

Hypofractionated scheme

Around 15 years ago, the first studies were designed to propose a hypofractionated treatment regimen (shorter treatment time with higher dose per fraction). One would be able to hypothetically optimize the treatment period using this promising technique. Thus, problems such as scarcity of RT services and equipment and poor access of patients coming from distant places to receive RT applications could be less important in the therapeutic decision. Additionally, hypofractionated treatment would reduce waiting lists in public healthcare, such as in Brazil.

A Canadian study[17] randomized 1,234 women submitted to conservative treatment, with negative resection margins and negative lymph nodes to receive 4250 cGy total dose in 16 fractions (22 consecutive days), or 5000 cGy in 25 fractions (35 consecutive days). With a median follow-up of 69 months, local recurrence-free survival at five years was similar between the two arms (97.2% vs. 96.8%) as well as overall and disease-free survival, with 77% of excellent or good cosmetic results in both arms. In this study update[18], with twelve years of follow-up, recurrence rates were similar: 6.7% for the standard treatment versus 6.2% for hypofractionated, with around 70% of excellent or good cosmetic results in both groups.

So this is a new model that can be used in selected patients, which must be avoided in situations where there was prior chemotherapy, when it is necessary to treat regional lymph nodes with RT, in immediate plastic reconstructions and in large breasts. The role of boost in hypofractionated schemes is uncertain, since at the time of the Canadian study design its real significance was not known. However, in the START British studies, use of boost as well as irradiation of the regional lymph nodes were allowed[19,20].

Partial breast irradiation

Based again on the rationale that the majority of recurrences after conservative treatment occurs in the primary tumor quadrant, combined with the social aspects mentioned above (distance from the residence to the RT service etc.), the possibility to perform RT directed only to the tumor bed and not to the whole breast in selected cases has been suggested and tested in studies with varying levels of evidence. This technique was named as accelerated partial breast irradiation (APBI).

Several techniques have been applied for APBI, from brachytherapy with high or low dose rates (intracavitary or interstitial), intraoperative RT (IORT) with electrons or orthovoltage or even external RT.

The American Society for Therapeutic Radiology and Oncology (ASTRO) in a recent publication[21] listed its normative consensuses concerning APBI, inferring the criteria and characteristics of patients that are candidates for this new therapeutic modality. This publication is considered the main guideline for APBI and it admits the treatment of some patients out of investigation protocols (Table 1).

Similarly, the Groupe Européen de Curiethérapie and European Society for Therapeutic Radiology and Oncology[22] also published their recommendations for APBI, categorizing patients into low risk, intermediate risk and high risk (good candidates, possible candidates and potential contraindications for APBI, respectively).

Table 1 – Patient selection for accelerated partial breast irradiation (APBI) according to the American Society for Therapeutic Radiology and Oncology (ASTRO)[21]

Criteria used	APBI		
	Suitable (all factors)	Cautionary (any factor)	Unsuitable (study protocols) (any factor)
Patient age	≥ 60 yrs.	50-59 yrs.	< 50 yrs.
Tumor size	Up to 2 cm	2 to 3 cm	> 3 cm
Histological type	IDC	ILC	DCIS
Histological/nuclear grade	Any	–	–
Lymphovascular invasion	Negative	Focal	Extensive
Estrogen receptor	Positive	Negative	–
DCIS/ intraductal extension	Not allowed	Up to 3 mm	> 3 cm
Surgical margins	Negative	< 2 mm	Positive
Presentation	Unicentric	–	–
Lymph node status	Negative	Negative	Positive
BRCA	Negative	–	Positive
Neoadjuvant CT	Not allowed	Not allowed	Yes

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; DCIS, ductal carcinoma in situ; CT, chemotherapy.

Perhaps the main benefit of using these techniques is to reduce the total treatment time, which rather than being performed for six weeks (conventional RT), can be carried out at the time of surgery to remove the tumor (IORT) or up to one week after the surgical procedure (brachytherapy). Although all the studies presented very promising results, follow-up of all series is relatively short and the treatment is applied only to highly selected patients.

Adjuvant radiotherapy in ductal carcinoma in situ

Ductal carcinoma in situ (DCIS) is traditionally classified taking the architectural pattern into account (comedonecrosis, cribriform, micropapillary, papillary or solid) and represents a distinct set of proliferative lesions with potential heterogeneous invasiveness. Thus, it is necessary to identify the lesions most likely to be aggressive in order to establish the appropriate treatment plan.

At the era of radical mastectomy, cure rates approached 98%. With the rise of conservative treatment for invasive carcinomas, this strategy was introduced and considered the standard approach for DCIS, although there have been no prospective randomized trials comparing radical mastectomy and conservative treatment in this specific population.

Three studies have shown the benefit of adding adjuvant RT in patients with DCIS undergoing breast-conserving surgery. The NSABP B-17 study[23] included 818 patients who were randomized between sole surgical treatment or surgery associated with whole breast RT with a total dose of 5000 cGy. The primary outcome was local, invasive or intraductal recurrence. With 12 years of follow-up, the use of RT reduced the cumulative local recurrence rate (16% versus 32%). When stratified in terms of invasive and non-invasive recurrences, this gain was observed in both subgroups, although the reduction was greater for the invasive than for the non-invasive ones (16.8% vs. 7.7% and 14.6% vs. 8%, respectively). There was no impact on overall and cancer-specific survival.

In another study of similar design (European Organization for Research and Treatment of Cancer - EORTC 10853)[24], 1,010 patients with DCIS treated with conservative surgery with tumors ≤ 5 cm were randomized between whole breast RT (dose of 5000 cGy) or clinical follow-up. After 4.3 years of follow-up, those who received RT had lower rates of invasive (4.8% vs. 8%) and non-invasive recurrence (5.8% vs. 8.8%) compared to those without adjuvant therapy.

The cooperative study (England - Australia - New Zealand)[25], of which update was presented at the 32nd San Antonio Breast Cancer Symposium[26] randomized 1,701 patients submitted to surgery for DCIS with clear margins in the following groups: surgery alone, surgery with RT, surgery with tamoxifen, surgery with radiotherapy and tamoxifen. After 53 months of mean follow-up, RT decreased the incidence of ipsilateral invasive disease (hazard ratio of 45%) and ipsilateral DCIS (hazard ratio of 36%). Use of hormone therapy did not reduce the incidence of ipsilateral invasive tumors, but decreased the overall DCIS recurrence (hazard ratio of 68%).

Although there are criticisms to the NSABP B-17 and EORTC 10853 studies due to the fact that pathologic and mammographic assessments are not in accordance with current standards, there is a clear advantage in using RT to reduce the risk of local recurrence when compared with surgery alone. There are no concrete data in the literature capable of selecting subgroups of patients with DCIS who would benefit little or not at all from RT after conservative surgery.

Molecular predictors of recurrence

Traditionally, the decision of the best approach for the treatment of patients with breast cancer is based on clinical and pathological characteristics and staging (TNM), surgical margin status, histology and patient age. However, with the increasing knowledge of molecular biology, the concept that breast cancer represents a heterogeneous group of diseases is increasingly accepted and researchers are now investigating whether these particular molecules could modify the employed therapeutic strategy.

The most recent classification of breast tumors with the participation of molecular biology tends to subdivide them into luminal categories A or B, HER-2 positive or negative and triple negative. Likewise, use of molecular predictors that assess gene expression could also be used in assessing the risk of local recurrence.

Although the first published studies helped in the decision regarding the type of adjuvant systemic treatment to be used, there are as yet no clinical trials that correlate the role of RT with molecular predictors of local and systemic recurrence[27, 28].

Conclusion

Indications and contraindications of adjuvant RT in the therapeutic approach of patients with early-stage breast cancer submitted to conservative treatment are well-defined in the literature. For selected patients, hypofractionated RT schemes or partial breast irradiation can be employed, as there is evidence that this option is equivalent in terms of local control to the classic model of breast irradiation.

Adjuvant RT in DCIS should be offered to all patients, especially younger ones, by reducing the risk of local recurrence. There are no concrete data in the literature capable of selecting subgroups of patients with DCIS who would benefit little or not at all from RT after conservative surgery.

Correlation between the role of RT with molecular predictors of local and systemic recurrence should be further studied.

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